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Short Commentary

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Neural Control of Dermatological Functions

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Abstract

As any other organs, the skin is controlled directly and indirectly by a variety of neural systems in mammals. One of the best known mechanisms is undoubtedly sensory transmission of signals associated with touch, temperature, pressure or pain sent to the spinal cord and other Central Nervous System (CNS) areas. However, additional mechanisms have been identified more recently in the control of other dermatological functions including maintenance of body temperature, of protection against infections, diseases and other external factors. This editorial aims at summarizing some of the most recent advance in motor and neuro-endocrine mechanisms involved in the neurological control of normal skin functions. These new findings may also shed some light on the underlying mechanisms oftemperature control, xerosis, pruritus, eczema, and psoriasis.

Dermatological functions

The skin interfaces with the environment and is the first line of defense from external factors. It prevents also excessive water loss and serves as an insulation barrier for the regulation of temperature. It allows also sensation and the production of vitamin D. The mammalian skin is composed of two main layers: the epidermis (outer layer) and the dermis (inner layer).The epidermis is a stratified squamous epithelium composed of proliferating basal and differentiatedsuprabasalkeratinocytes. Keratinocytes are the major cells, constituting 95% of the epidermis whereas the remaining is composedof Merkel cells, melanocytes and Langerhans cells [1]. The epidermis can be further subdivided into other layers (e.g: stratum lucidum, granulosum, spinosum, germinativum) - none of which contains blood vessels although the deepest layers are 'nourished' by diffusion from blood capillaries extending to the upper layers of the dermis. The epidermis and dermis are separated by the basement membraneconstituted of cells from both tissues that serve also to bind cytokines and growth factors, as a reservoir for their controlled release during repair processes [2,3]. The dermis provides strength and elasticity to the skin through an extracellular matrix composed of collagen fibrils, microfibrils, and elastic fibers, embedded in hyaluronan and proteoglycans [4]. It harbors many mechanoreceptors, thermoreceptors and nociceptors that provide the sense of touch, pressure and heat. It also contains hair follicles, sweat,sebaceous and apocrine glands, as well aslymphatic and blood vessels. Blood vessels in the dermis nourish and remove wastes from its own cells as well as for the epidermis.

The sensory function of the skin is rather well understood. Cutaneous nerves and sensory elements of the Peripheral Nervous System (PNS) respond to stimuli from the circulation and to emotions ("internal trigger factors"). Moreover, the CNS is directly (via efferent nerves or CNS-derived mediators) or indirectly (via the adrenal glands or immune cells) connected to skin function.Sensory as well as autonomic (sympathetic) nerves influence a variety of physiological (embryogenesis, vasocontraction, vasodilatation, body temperature, barrier function, secretion, growth, differentiation, cell nutrition, nerve growth) and pathophysiological (inflammation, immune defense, apoptosis, proliferation, wound healing) functions within the skin. In unstimulated nerves, neuromediators are barely detectable within the skin tissues. Upon direct stimulation by physical stimuli (thermal, ultraviolet light, mechanical, electrical), chemical, or indirect stimuli such as allergens, microbiological agents, trauma, or inflammation, a significant increase of regulatory neuropeptides, neurotrophins, neurotransmitters, or oxygen products (e.g., nitric oxide) can be detected in vitro and in vivo. Thus mediators derived from sensory or autonomic nerves may play an important regulatory role in the skin under many physiological and pathophysiological conditions. Beside the periphery,

however, a complex communication network exists between the spinal cord, the CNS, and the immune endocrine system.

Neural control of motor system-regulated blood flow to the glabrous skin is an important mechanism determining heat exchanges between the body and the environment, and thus contributes to thermoregulation. Increasing blood flow to the skin by cutaneous vasodilatation enhances heat dissipation from the skin surface, a part of the heat-defense response. Decreasing skin blood flow by cutaneous vasoconstriction greatly contributes to accumulation of central core heat, as a part of the cold-defense response or of the fever response.Nakamaura and Morrison recently discovered thermal afferent pathways activated by thermoreceptors that convey temperature signals from the periphery to the thermoregulatory center in the preoptic area [5].

Indirect neural control via neuroendocrine responses has been associated with cutaneous vascular systems being either dilated or constricted by hormoneswhich release is under CNS control. In response to acute thermoregulatory or aversive events such as cold or alerting stimuli, neural influence is predominant. Arterio Venous Anastomoses (AVAs) play a key role in cutaneous blood flow regulation -dilating AVAs for low-resistance bypasses, which increase cutaneous vascular volume enabling more blood to the skin [6]. The AVAs, abundant in hairless skin areas, are densely innervated by sympathetic nerve fibersthat release noradrenaline which, in turn, binds toα-adrenergic receptors on cutaneous vascular smooth muscle for cutaneous vasoconstriction [7].

Vasomotor responses are elicited by cold/heat exposure, pyrogenic substance or by alerting stimuli. The medullary rapheandpreoptic areas that contains sympathetic premotor neurons control cutaneous vasomotor activity and thermoregulatory and fever responses,respectively. The importance of the medullary raphenucleus in controlling cutaneous vasomotor activity was clearly pointed out by Blessing and colleagues who showed that disinhibition of neurons in the medullary raphe with bicuculline ((γ-aminobutyric acid (GABA)A receptor antagonist)) can stronglyproduce vasoconstriction in the rat tail whereas inhibition of medullary raphe neurons causes vasodilatation of in the same area [8].

The Rostral Ventrolateral Medulla Oblongata (RVLM) contains sympathetic premotor neurons for the cardiovascular system, controlling vasoconstriction, heart rate and arterial pressure. RVLM neurons are also involved in vasoconstriction since its electrical stimulation reduces tail temperature, indicating cutaneous vasoconstriction whereastheir inhibition increases ear pinna blood flow [9,10].

The preoptic area contains neurons responding to local brain, core and skin temperature. Its stimulation with heat leads to cutaneous vasodilatation in the rat tail [11]. Other CNS areas such as the dorsomedial hypothalamus,the ventral tegmental area and the periaqueductal gray matter area are also involved in cutaneous vasodilation and vasoconstriction whereas serotoninis also involved in vasomotor control -the 5-HT1A receptors considered to be inhibitory somatodendritic autoreceptors, are expressed mainly on 5-HT cells (e.g., raphe neurons, smooth muscles surrounding blood vessels), although the receptors are also present on non-5-HT cells [12].

Wetness is experienced when the skin is in contact with a wet surface or when sweat is produced through a complex multisensory integration of thermal (i.e., heat transfer) and tactile (i.e., mechanical pressure and friction) inputs generated by the interaction between skin, moisture, and (if donned) and clothing. The hypothesis of wetness as a "perceptual illusion" shaped by sensory experience has been supported by recent findings showing that exposing the skin to cold-dry stimuli (resulting in cooling rates similar to those occurring during the evaporation of water from the skin) can evoke an illusion of local skin wetness [13].

Pruritus(itch) is a predominant symptom of many cutaneous disorders like eczema. Electrocutaneous stimulation of afferent nerves has shown that increased frequencies leads to more intense pruritus or pain without any qualitative change in the sensation from one modality to the other. Oral antihistamines although standardly prescribed against pruritus are generally ineffective in the treatment of many types of pruritus, suggesting a role for non-histaminic pathways[14,15]. Among them, mechano-responsive C fibers, but not mechano-insensitive C fibers (CMi), activated by cowhage. This is in contrast to histamine inducing itch only in mechano-insensitive fibers which, in turn, suggests that separate non-overlapping groups of C fibers may underlie different types of pruritus. Since cowhage spicules contain a cysteine protease, mucuna in which is a pruritogenic substance that binds to proteinase-activated receptors, PAR 2 and PAR 4,this also suggests that drugs capable of blocking the cowhage pathway may be ideally suited as new treatment against some forms of chronic pruritus [16,17].

Other promising areas of research include interleukin-17 inhibitors against psoriasis [18], isotretinoin against rosacea [19] orμ-opioid receptor antagonists andκ-opioid receptor agonists against pruritus [20]. Until new CNS or PNS drugs get identified, developed and approved by authorities, patients with some of the dry skin-related problems can use recently developed and scientifically-based topical creams that potently treat and prevent skin dryness and damage [21,22] All in all, several new cellular targets involved in skin functions and dysfunctions have been unraveledin recent years which suggeststhat new drug candidates shall soon be identified and developed as promising new drug treatments for skin health.

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